

Adjusting the Focus on Transfusion-associated Circulatory Overload

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TRANSFUSION-ASSOCIATED circulatory overload (TACO) remains the most common pulmonary complication of transfusion and the second most common cause of transfusion-related deaths reported to the Food and Drug Administration.¹ The term TACO was coined by Popovskiy² in 1983 and is characterized by new or worsening hydrostatic pulmonary edema occurring within 6 h of blood transfusion. Its incidence, especially in perioperative settings where approximately one quarter of blood components is transfused, has historically been underestimated due to passive reporting. However, with the advent of electronic health records, we have seen advances in algorithms to screen and identify cases of posttransfusion pulmonary edema. Toy *et al.*^{3,4} pioneered such algorithms in their study of transfusion-related acute lung injury at the University of California San Francisco (San Francisco, California), and the Mayo Clinic group has used them to study the epidemiology of pulmonary transfusion reactions. In this issue, Clifford *et al.*⁵ characterize risk factors and associated outcomes related to perioperative TACO.

While previous work has focused on risk factors in intensive care or mixed medical/surgical populations, the current study is novel in that it focuses squarely on a noncardiac, perioperative population that is known to be at high risk for pulmonary complications of transfusion. The authors also used a granular dataset that allowed for the inclusion of both intravenous fluid and blood component administration in their multivariable analyses. As such, many patient-specific risk factors, such as estimated circulating blood volumes, duration of surgery, and estimated blood



“Why is better recognition and prevention of transfusion-associated circulatory overload important?”

loss, were not found to be significant for TACO after controlling for total fluid administered. Not surprisingly, emergency surgery, where aggressive therapeutics including transfusion are often necessary to maintain hemodynamics and control hemorrhage, was associated with an increased risk of TACO in patients with impaired cardiorenal function. However, Clifford *et al.*⁵ found that preoperative documentation of congestive heart failure correlated poorly with echocardiographic abnormalities. Thus, the broader use of preoperative echocardiography, especially in a noncardiac population, may be critical in identifying high-risk patients. In emergency surgery, presurgical β -blocker use may be a surrogate for underlying cardiac or kidney disease not identified before surgery.

Clifford *et al.*⁵ and previous work suggest that sensitive electronic algorithms to detect TACO are currently feasible.³⁻⁵ Unfortunately, surveillance criteria for TACO, which are based on the presence of one or more signs or symptoms of pulmonary edema, lack specificity and require expert review as part of case adjudication. Further research in anesthesia and critical care medicine may lead to the elaboration of more precise diagnostic criteria for or to systematically exclude TACO, transfusion-related acute lung injury, and other causes of perioperative pulmonary edema. The addition of specific clinical risk factors, such as those described by Clifford *et al.*⁵ to natural language processing algorithms to automatically review free-text in chest radiograph and clinical reports may improve the specificity of electronic surveillance for TACO.

Image: J. P. Rathmell.

Corresponding article on page 409.

Accepted for publication October 28, 2016. From the Blood Systems Research Institute, San Francisco, California (N.R., E.L.M.); Kaiser Permanente Division of Research, Oakland, California (N.R.); and Departments of Laboratory Medicine and Epidemiology/Biostatistics, University of California San Francisco, San Francisco, California (E.L.M.).

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What are the implications for future research? Additional translational research is needed in the pathophysiology of TACO as well as the assessment of biomarkers in its diagnosis. Could there be a component of alveolar damage in its pathogenesis or is it entirely explained by transudation of fluid into the alveoli due to elevated pulmonary venous pressures? Recent studies examining the role of vital signs and cytokines in TACO suggest that its pathophysiology may not be entirely hemodynamic.^{6,7} To help answer these questions, Kor *et al.* are currently leading a clinical trial of the effect of washed blood components on inflammatory markers and the occurrence of TACO (ClinicalTrials.gov ID: NCT02094118).

Why is better recognition and prevention of TACO important? Despite the notion that transfusion-associated volume overload can be treated easily and carries little morbidity, both Clifford *et al.*⁵ and Murphy *et al.*⁸ found increased in-hospital mortality and prolonged ICU and hospital length of stay after pulmonary edema in patients who developed TACO compared to that of transfused controls. This morbidity burden and increased length of stay is certainly associated with higher hospital costs—a real concern in the current medical economic landscape in the United States. Further studies focused on the prevention and treatment of TACO also fit well with hemovigilance efforts to identify and mitigate transfusion-related complications. In other words, should TACO be considered a preventable complication and a measure of healthcare quality? In order to minimize indication bias as contributing to increased morbidity, future studies should control for American Society of Anesthesiologist physical status classification and other comorbidities.

For the practicing physician, one could imagine the development of interventions by which real-time predictive algorithms would alert physicians *via* the electronic health record to patients at increased probability of TACO, allowing preventive measures in high-risk patients. Similar alert systems have been developed for patients at risk of decompensation and transfer to the intensive care unit using automated screening of clinical data and comorbid medical conditions.⁹ In the current study, two thirds of TACO cases underwent nonemergent surgery, suggesting ample opportunity to prevent adverse outcomes such as TACO. Clinical decision support systems incorporating relevant vital signs such as a patient's historical pulse pressure or creatinine clearance could further alert anesthesiologists to patients at high risk of developing TACO perioperatively. As an example, one study found that a simple TACO risk score incorporating age, a history of congestive heart failure, and renal dysfunction led to a smaller volume of transfused products in higher risk patients.¹⁰

The principles of patient blood management—optimizing preoperative erythropoiesis, reducing operative blood loss, and optimizing physiologic tolerance of anemia—are also relevant to the article by Clifford *et al.*⁵ As patient blood management is more widely adopted, it is likely to diminish the overall incidence of TACO if not necessarily the incidence per transfused patient, as suggested by a recent study by the same authors.⁴

Thus, the incidence of TACO is likely to be a moving target as patient blood management reduces blood utilization and TACO incidence in the United States. Other than transfusing less, can the detection of patients at high risk of TACO be accompanied by other effective preventive measures? As reviewed above, there are little data beyond that in the general pulmonary edema literature on the efficacy of specific prevention and treatment interventions for TACO. Potential interventions include single-unit erythrocyte orders, slower infusion rates, prophylactic diuretic administration (when, which diuretics, and what dosing?), and the use of alternatives to plasma transfusion such as coagulation factor concentrates to reverse anticoagulation. Anesthesiologists can play a critical role in preoperative screening for risk factors for TACO, as well as improving perioperative monitoring and management.

In conclusion, the study by Clifford *et al.*⁵ and other recent work have significantly expanded our knowledge about the incidence of and risk factors for perioperative TACO, but a number of research questions remain. In addition to corroborating these findings, some of these questions may be answered by a large case-control study currently being conducted as part of the National Heart Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III Serious Transfusion Reactions Including Pulmonary Edema study. But other questions will require translational research to test novel strategies in the prevention and treatment of TACO.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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Civil War Chloroform Tin from a U.S. Army Coolidge Carrier Set



Richard H. Coolidge, M.D. (1816 to 1866), served the U.S. Army as an assistant surgeon and medical inspector. In 1863, he designed a compact field case, the U.S. Army Surgeon's Field Companion (or "Coolidge Carrier Set"), which housed needles, sutures, bandages, and tins of essential pharmaceuticals such as ginger, ipecac, opium, quinine, and chloroform (*left*). This 8-ounce tin was marked "CHLOROFORMUM" (*right*) and labeled as "Prepared at the / U.S.A. [United States Army] Laboratory / Philadelphia / Pa. / 1863." Because this tin was inspected officially, it bore the coat of arms of the U.S. Army Medical Department, with the cockerel of vigilance cresting an escutcheon bearing the staff of Aesculapius (sinister) and the 20-star U.S. flag (dexter) from the 1818 year of departmental founding, all surmounting the Latin motto *Experientia et Progressus*. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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